Complete Summary

GUIDELINE TITLE

Guidelines for the use of prophylactic anti-D immunoglobulin.

BIBLIOGRAPHIC SOURCE(S)

Parker J, Wray J, Gooch A, Robson S, Qureshi H. Guidelines for the use of prophylactic anti-D immunoglobulin. London (UK): British Committee for Standards in Haematology (BCSH); 2006. 13 p. [21 references]

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previously published version: Lee D, Contreras M, Robson SC, Rodeck CH, Whittle MJ. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. Transfusion Medicine. 1999; 9:93-7.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Hemolytic disease of the newborn (HDN)
- Rh alloimmunization

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide healthcare professionals with practical guidance on the use of anti-D immunoglobulin as immunoprophylaxis to prevent sensitisation with anti-D
- To update the previous recommendations of 1999 on the administration of anti-D
- To take into account the National Institute for Health and Clinical Excellence (NICE) publications and recommendations

TARGET POPULATION

- Pregnant women in the United Kingdom who are blood type RhD negative
- D-negative premenopausal females who are given D-positive blood components

INTERVENTIONS AND PRACTICES CONSIDERED

Management

1. Record keeping (documentation, audit trail)
2. Informed consent
3. Identification of sensitizing events
4. Assessment of anti-D sensitivity (acid elution, flow cytometry, direct antiglobulin test)
5. Assessment of feto maternal haemorrhage
6. Staff training
7. Patient education
8. Use of the routine antenatal anti-D prophylaxis scheme
9. Pretransfusion antibody screening

Treatment/Prophylaxis

1. Anti-D preparations (D-GAM®, Partobulin SDF®, Rhophylac®, WinRho SDF®)
2. Dose and route of administration (intramuscular, intravenous)
3. Site of administration
4. Timing of administration (before 12 weeks, between 12 to 20 weeks, after 20 weeks of gestation; following birth)
5. Frequency of administration

6. Reversal of inadvertent transfusion of D positive blood to a D negative pre-menopausal female

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality
- Sensitization rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A search of published literature was undertaken using PubMed, Cochrane Library and Ingenta databases. The following key words were used: anti-D, pregnancy, antenatal, prophylaxis, rhesus, and RhD. This covered the period 1999-2004. The papers included were subjected to critical reading by the authors using the Critical Appraisal Skills Programme (CASP) appraisal tool and were ranked according to the hierarchy of evidence. This approach took account of the National Institute for Health and Clinical Excellence (NICE) systematic review undertaken in 2000 so as to be contemporary in locating and including the relevant literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed controlled study without randomization

IIb Evidence obtained from at least one other well-designed quasi-experimental study

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The papers included were subjected to critical reading by the authors using the Critical Appraisal Skills Programme (CASP) appraisal tool and were ranked according to the hierarchy of evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guideline group was selected to be representative of UK based medical experts and patients' representatives.

The writing group produced the draft guideline which was subsequently revised by consensus by members of the Transfusion Task Force of the British Committee for Standards in Haematology.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation

Grade A (evidence levels Ia, Ib) Requires at least one randomised controlled trial as part of the body of the literature of overall good quality and consistency addressing the specific recommendation

Grade B (evidence levels IIa, IIb, III) Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation

Grade C (evidence level IV) Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was reviewed by a sounding board of United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology (BSH) Committee and comments incorporated where appropriate.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendation grades (**A-C**) and levels of evidence (**Ia-IV**) are defined at the end of the "Major Recommendations" field.

Administration of Anti-D Immunoglobulin

1. Documentation accompanying the injection must include a report containing the following details:
    - Identity of the patient to include surname, forename, date of birth and a unique ID number with the date when the injection is to be given. (**Level IIa, Grade B**).
    - Identity and address of the general practice (GP) surgery/antenatal clinic administering the injection. (**Level IIa, Grade B**).

    Details of the injection will include batch number and strength of dose and route of administration.

2. The details of the administration of anti-D must be recorded in the antenatal record. It is also important that these details are centrally recorded in the hospital blood bank computer so that this information is readily available should pre-transfusion testing be required.

Prevention of Antibody Formation

3. If the pregnancy is non-viable and no sample can be obtained from the baby, prophylactic anti-D should be administered to the woman, if she is D-negative. (**Level IV, Grade C**).
4. Following sensitising events anti-D should be injected as soon as possible and certainly within 72 hours of the event. However if this deadline cannot be met due to exceptional circumstances, some protection may be offered up to 10 days after the sensitising event (Lee et al., 1999; Royal College of Obstetricians and Gynaecologists [RCOG], 2002). (**Level III Grade B**).
5. It is essential to assess the volume of feto maternal haemorrhage (FMH) to calculate the appropriate anti-D dosage for administration. (**Level IIb, Grade B**).

Management of a Routine Prophylaxis Scheme

6. The routine antenatal anti-D prophylaxis (RAADP) scheme should be regarded as supplementary to any anti-D administered for the following sensitising episodes (RCOG, 2002). (**Level IIb Grade B**):

   Amniocentesis

   Cordocentesis

   Other in-utero therapeutic intervention/surgery (e.g., intrauterine transfusion, shunting)

   Ante partum haemorrhage (APH)

   Chorionic villus sampling

   Ectopic pregnancy

   External cephalic version

   Fall/abdominal trauma

   Intrauterine death

   Miscarriage

   Termination of pregnancy

7. It is important that the 28-week antibody screening sample is taken prior to the first routine prophylactic injection being given. This forms the second screen required in pregnancy in the National Guideline Clearinghouse (NGC) summary of the British Committee for Standards in Haematology (BCSH) Guidelines for Blood Grouping and Red Cell Antibody Testing in Pregnancy. (Gooch et al., 2006) (**Level III, Grade B**).

Pretransfusion Antibody Screening

8. The specificity of anti-D detected post-injection should be confirmed using a panel of D negative reagent cells. This test should also be used to establish the presence or absence of any other clinically significant antibodies, especially in transfused patients. See the NGC summary of the BCSH Guidelines for Blood Grouping and Red Cell Antibody Testing in Pregnancy. (Gooch et al., 2006) (**Grade B**).
9. If there is a record of anti-D injection within the past eight weeks and the level is below 1 international unit per milliliter (iu/mL) a further sample should be tested at 28 weeks and prophylaxis should continue. If there is no record of anti-D injection the antibody should be monitored as for immune anti-D i.e., at four weekly intervals to 28 weeks and at fortnightly intervals thereafter. If the anti-D level is falling, it is probably passive whereas if it is steady or rising it is probably immune. Prophylactic anti-D should continue in either case unless it is established that the anti-D is immune. (Gooch et al., 2006) (**Level IIb, Grade B**).

Prevention of Anti-D Formation in the Event of Recurrent Uterine Bleeding in D- Negative Women During Pregnancy

Recurrent Uterine Bleeding Before 12 Weeks Gestation

Anti-D immunoglobulin is not necessary in women with threatened miscarriage with a viable fetus where bleeding completely stops before 12 weeks gestation. However, it may be prudent to administer 250 iu anti-D Immunoglobulin where bleeding is heavy or repeated or where there is associated abdominal pain, particularly if these events occur as gestation approaches 12 weeks (**Level IV, Grade C recommendation**). The period of gestation should be confirmed by ultrasound.

Recurrent Uterine Bleeding Between 12 and 20 Weeks Gestation

D-negative women with recurrent PV bleeding between 12 and 20 weeks gestation should be given 250 iu anti-D immunoglobulin at a minimum of 6 weekly intervals (**Level IV, Grade C**).

Recurrent Uterine Bleeding after 20 Weeks Gestation

Anti-D immunoglobulin 500 iu should be given at a minimum of 6 weekly intervals. Estimation of FMH by acid elution technique should be carried out at 2 weekly intervals. If the 2 weekly FMH is positive, additional dose of anti-D immunoglobulin (500 iu minimum, more if FMH exceeds 4 mLs) should be offered regardless of the presence or absence of passive anti-D in maternal plasma, and FMH should be retested after 72 hours (**Level IV, Grade C**).

Management of Transfusion of D-Positive Blood Components

D Positive Platelet Transfusions

Whenever possible, D negative platelets should be transfused to D negative pre-menopausal women who need a platelet transfusion. Occasionally, if the appropriate product is not available or would cause unacceptable delay, it may be necessary to transfuse D positive platelets. In these circumstances, prophylaxis against possible Rh alloimmunisation by red cells contaminating the platelet product should be given (Menitove, 2002).

A dose of 250 iu anti-D immunoglobulin should be sufficient to cover up to five adult therapeutic doses of D positive platelets given within a 6 week period (BCSH, 2003) (**Grade B**). In severely thrombocytopenic patients with platelet counts of less than 30 x 10^9/L, anti-D should be given subcutaneously to avoid the risk of haematoma following intramusculary (i.m.) injection. It is not necessary to administer anti-D immunoglobulin to D-negative females without childbearing potential, or males who receive D positive platelets (BCSH, 2003; Menitove, 2002).

Inadvertent Transfusion of D Positive Blood to D Negative Pre-Menopausal Females

When less than 15 mL have been transfused, the appropriate dose of anti-D immunoglobulin should be given. When more than 15 mL have been transfused, it is preferable to use the larger anti-D immunoglobulin i.m. preparation (2500 iu). The dose should be calculated on the basis that 500 iu of anti-D will suppress sensitisation by 4 mL of D positive red cells (RCOG, 2002).

When two units or more of D-positive blood have been transfused, a red cell exchange transfusion should be considered to reduce the load of D positive red cells in circulation and the dose of anti-D immunoglobulin required to suppress immunisation. In this situation, the patient should be counselled regarding the implications of both non-intervention (for future pregnancies) and of treatment, including any hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D including intravenous anti-D (RCOG, 2002).

A single blood-volume red cell exchange transfusion will achieve a 65 to 70% reduction in D-positive red cells; a double volume exchange will achieve an 85 to 90% reduction. Shortly after the exchange transfusion, the residual volume of D-positive red cells should be estimated using flow cytometry. Intravenous anti-D Immunoglobulin is the preparation of choice, achieving adequate plasma levels immediately and being more effective microgram for microgram at clearing red cells. The dose to be administered should assume that 600 iu of anti-D i.v. will suppress immunisation by 10 mL fetal red cells. Intramuscular preparations of anti-D immunoglobulin must not be given intravenously. An appropriate combined dose of i.v. and i.m. anti-D should be determined in discussion with a specialist in Transfusion Medicine. Follow-up tests for D positive red cells should be undertaken every 48 hours and further anti-D given until there are no detectable D positive red cells in circulation.

Free anti-D in mother's serum does not necessarily reflect adequate prophylaxis and anti-D immunoglobulin treatment should be continued until D positive red cells are no longer detectable (RCOG, 2002).

Passive anti-D given in large doses may be detectable for up to 6 months or longer, and tests for immune anti-D may not be conclusive for several months.

Table: Recommendations for Antenatal and Postnatal Tests and the Prevention of Sensitisation

Gestation	Summary of Tests and Treatment
<12 weeks	No action for uncomplicated miscarriage or painless vaginal bleeding. In all other cases check ABO and D type to confirm D negativity. Confirm absence of anti-D. Issue and administer 250 iu anti-D, intramuscularly (i.m.)
12 weeks | 20 weeks	For all potentially sensitising episodes ABO and D type to confirm D negativity. Confirm absence of immune anti-D. Issue and administer 250 iu anti-D, i.m.

Gestation	Summary of Tests and Treatment
20 weeks	For all potentially sensitising episodes ABO and D type to confirm D negativity. Confirm absence of immune anti-D. Assess FMH. Issue and administer at least 500 iu anti-D, i.m., depending on the size of FMH.
28 weeks	**First RAADP** Issue and administer at least 500 iu prophylactic anti-D. The routine sample for blood group and antibody screen as required by BCSH Guidelines (see the NGC summary of the BCSH Guidelines for Blood Grouping and Red Cell Antibody Testing in Pregnancy) (Gooch et al., 2006) **must** be taken prior to this injection.
34 weeks	**Second RAADP** Issue and administer at least 500 iu anti-D.
BIRTH	TESTS ON BABY – Establish ABO and D type. MATERNAL TESTS – Check ABO and D type. Assess FMH if baby is D positive. Issue and administer at least 500 iu anti-D to the mother if baby is D positive. More anti-D may be required depending upon the size of any FMH.

Definitions:

Level of Evidence

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations.")

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Prior to 1970 haemolytic disease of the newborn (HDN) due to anti-D was a significant cause of morbidity and mortality. By 1990, a reduction in mortality from 1.2 per 1000 births to 0.02 per 1000 births had been achieved in response to the introduction of immunoprophylaxis with anti-D immunoglobulin. During that time the sensitisation rate dropped to about 1.2%. A further reduction to between 0.17 to 0.28% was achieved by introducing prophylaxis during the third trimester of pregnancy.

POTENTIAL HARMS

Hazards or red cell exchange transfusion include hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D including intravenous anti-D.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Audits of practice should to be undertaken on a continuing basis to ensure compliance with these guidelines and, where identified, variance or concerns in relation to compliance should be addressed.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Parker J, Wray J, Gooch A, Robson S, Qureshi H. Guidelines for the use of prophylactic anti-D immunoglobulin. London (UK): British Committee for Standards in Haematology (BCSH); 2006. 13 p. [21 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 (revised 2006)

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

Writing Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Writing Group: Parker J, Department of Haematology, Derby City Hospital, Derby; Wray J, University of Salford, Salford, Greater Manchester; Gooch A, National Blood Service, Manchester; Robson S, School of Surgical and Reproductive Sciences, University of Newcastle upon Tyne; Qureshi H, Department of Haematology, University Hospitals of Leicester, Leicester, UK

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None of the authors have declared a conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previously published version: Lee D, Contreras M, Robson SC, Rodeck CH, Whittle MJ. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. Transfusion Medicine. 1999; 9:93-7.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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